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Editorial Letter

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Exploring the Enigma of VEXAS Syndrome: A New Frontier in Medicine

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Abstract

In the realm of modern medicine, the discovery of novel diseases often presents both challenges and opportunities. VEXAS syndrome, an acronym for Vacuoles, E1 enzyme, X-linked, Autoinflammatory, Somatic syndrome, is a striking example of a unique monogenic disorder that has recently come to light. This syndrome represents a bridge between the worlds of rheumatology and hematology, and its clinical manifestations have left clinicians and researchers perplexed. In this editorial, I will delve into the complexity of VEXAS syndrome, exploring its clinical features, genetic underpinnings, and the quest for effective treatments. Furthermore, I will discuss how VEXAS syndrome may serve as a prototype for a new class of diseases that blur the boundaries between hematopoiesis and inflammation.

Keywords: VEXAS syndrome; hemato-inflammatory diseases; multisystem inflammatory involvement

Editorial Letter

VEXAS syndrome is characterized by myriad clinical features that span the realms of rheumatology and hematology. It presents a complex puzzle for clinicians due to its systemic inflammation, which affects various tissues and organs, including the skin, lungs, blood vessels, and cartilage. The multisystem involvement often results in confusing clinical diagnoses, including sweet syndrome, relapsing polytonicities, polyarteritis nodosa, and giant cell arteritis. Moreover, patients with VEXAS syndrome face various hematologic problems, such as macrocytic anemia, thrombocytopenia, thromboembolic disease, and progressive bone marrow failure. This progression towards bone marrow failure can ultimately lead to the development of hematologic malignancies, most notably myelodysplastic syndrome (MDS) [1, 2].

One intriguing aspect of VEXAS syndrome is its association with myeloid-driven inflammation, often refractory to treatment. This refractoriness poses a significant challenge for clinicians seeking effective therapeutic strategies. Furthermore, diagnosing VEXAS syndrome can be elusive, usually considered only after other treatment-refractory inflammatory diseases have been ruled out. Recent research suggests that certain clinical markers, such as male sex, mean corpuscular volume greater than 100fL, or platelet count less than 109/L, can aid in predicting VEXAS syndrome with remarkable accuracy [3].

The genetic underpinning of VEXAS syndrome is rooted in somatic mutations in the UBA1 gene, which encodes the ubiquitin-activating enzyme. These mutations are acquired later in life and are predominantly found in hematopoietic progenitor cells, particularly within the myeloid lineage. Notably, UBA1 is an X-linked gene that escapes X inactivation, which explains why VEXAS syndrome has, thus far, exclusively affected men. The initial discovery of VEXAS syndrome revealed that all affected individuals had missense mutations in codon 41 of UBA1. However, subsequent research has unveiled additional UBA1 mutations that expand our understanding of this syndrome. Some patients were found to have mutations in the splice motif at the junction of intron 2 and exon 3, resulting in a UBA1 protein lacking methionine 41. Another novel variant was identified, leading to temperature-dependent impairment of the resulting UBA1 isoform. These genetic insights further underscore the complexity of VEXAS syndrome and its heterogeneous nature [4].

One striking characteristic of VEXAS syndrome is the presence of vacuoles in myeloid and erythroid

precursor cells. Vacuoles are abnormal in these cells and are predominantly located in promyelocytes, myelocytes, erythroid precursors, and blasts within the bone marrow. These vacuoles are a hallmark feature of VEXAS syndrome and play a crucial role in its diagnosis. Notably, the presence of vacuoles in these cells is a key differentiator from other causes of myeloid and erythroid precursor cell cytoplasmic vacuolization. Identifying these vacuoles through morphologically examining bone marrow samples has become critical in the diagnostic process [5].

The link between VEXAS syndrome and hematologic malignancies, particularly myelodysplastic syndrome (MDS), is a significant concern. Multiple reports have highlighted a high incidence of MDS in VEXAS syndrome patients, which raises questions about the underlying mechanisms. Notably, the risk of developing MDS with acquired UBA1 mutations appears much higher than in other clonal hematopoietic diseases. This suggests that UBA1 may play a unique role in the pathogenesis of myeloid neoplasms. Furthermore, VEXAS syndrome has been associated with an increased risk of multiple myeloma (MM) in some cases. The overlap between VEXAS syndrome, MDS, and MM underscores the need for enhanced screening for these malignancies in affected individuals, particularly as more patients are identified at earlier stages of the disease [2].

The treatment of VEXAS syndrome poses a formidable challenge due to its refractoriness to conventional therapies. High-dose glucocorticoids, while temporarily alleviating symptoms, come with substantial toxicity and do not provide a long-term solution. Current treatment strategies involve various Immunosuppressive pharmacotherapies, yet the outcomes still need to be more satisfactory. However, tocilizumab, an IL-6 receptor blocker, has shown potential in controlling systemic inflammation in VEXAS syndrome. Azacytidine, a hypomethylating agent, has shown promise in some patients but does not consistently improve cytopenia or myelodysplastic features in bone marrow. Janus kinase inhibitors have effectively managed certain aspects of the systemic inflammatory disease associated with VEXAS syndrome, especially skin involvement. However, the lack of prospective clinical trials has hindered the establishment of optimal treatment approaches. Supportive care is essential to improve the quality of life for VEXAS patients. Nuances in the clinical phenotype of VEXAS syndrome may guide tailored treatment strategies, such as considering hypomethylating agents for patients with concurrent MDS [6].

As we navigate the complex landscape of VEXAS syndrome, it becomes evident that this condition is not merely an isolated medical curiosity but may represent a prototype for a new class of diseases. These diseases, tentatively called "hemato-inflammatory diseases," are characterized by somatic mutations in hematopoietic cells, systemic inflammation, and the potential to evolve into myelodysplastic, myeloproliferative, or lymphoproliferative disorders. Similar to VEXAS syndrome, these diseases blur the lines between rheumatology and hematology and challenge our traditional understanding of disease classification. In the broader context of medicine, VEXAS syndrome is a valuable reminder of the intricate interplay between clonal hematopoiesis and systemic inflammation. This interplay extends beyond VEXAS syndrome and encompasses various diseases where somatic mutations drive complex, adult-onset conditions. Understanding these connections is vital for both clinical management and research endeavors.

In conclusion, VEXAS syndrome represents a remarkable confluence of clinical, genetic, and therapeutic challenges. The dedication of researchers and clinicians to unravel its mysteries and develop effective treatments is commendable. As we continue to delve into the depths of VEXAS syndrome, we should remain open to the possibility that it may lead us to a deeper understanding of the complex web of hemato-inflammatory diseases. These diseases, in turn, may hold the key to novel therapeutic strategies and shed light on the intricate workings of our immune system and hematopoietic processes. The future of medicine is filled with promise, and VEXAS syndrome may be the gateway to a new frontier in healthcare.

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